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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JASPER RINE and MATTHEW ASHBY

Appeal 2008-1870
Application 10/038,206
Technology Center 1600

Decided: August 7, 2008

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

McCOLLUM, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 of the obviousness rejections of claims 38-85. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Claims 38-85 are pending and on appeal. We will focus on claims 38 and 49, which read as follows:

38. A method for analyzing the effects of subjecting a living thing to a stimulus comprising:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the plurality of units confines a probe comprising a pre-determined sequence of nucleotides, and wherein each of said pre-determined sequences is hybridizable with a different identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

(b) transducing the physical signals into electrical output signals,

(c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene, and

(d) analyzing the effect of said stimulus on said living thing by comparing the stored output signal data structure with an output signal data structure database, wherein the output signal data structure database comprises a plurality of output signal data structures stored in a computer memory.

49. The method of claim 38 wherein the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the genes of said living thing, or with transcripts of at least 0.5% of said genes, or with the cDNA derived from at least 0.5% of said genes.

Claims 38-53, 55-66, 68-83, and 85 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Gress,[1] Granelli-Piperno,[2] and either Fodor '98[3] or Fodor '91[4] (Ans. 3).

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Gress, Granelli-Piperno, either Fodor '98 or Fodor '91, and Watson[5] (*id.* at 7).

The Examiner relies on Gress for disclosing "a general method of assaying patterns of transcription by use of labeled total cDNA from mouse, and human cells by use of a cDNA X-Y coordinate grid array of probes spotted to form an array on a membrane" (*id.* at 4). The Examiner finds that the "array provides an optical signal of expression" and that Gress "shows importing the resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database" (*id.*). The Examiner also finds that Gress shows "that their high density array allows for the efficient assay of thousands of clones simultaneously" and "that their technique can be correlated with transcriptional, sequence, and genomic mapping information in a relational database" (*id.* at 4-5). In addition, the Examiner finds that

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[1] Thomas M. Gress et al., *Hybridization fingerprinting of high-density cDNA-library arrays with cDNA pools derived from whole tissues*, 3 MAMMALIAN GENOME 609-619 (1992).
[2] A. Granelli-Piperno et al., *Lymphokine and Nonlymphokine mRNA Levels in Stimulated Human T Cells*, 163 J. EXP. MED. 922-937 (1986).
[3] US 5,800,992, Sep. 1, 1998.
[4] Stephen P. A. Fodor et al., *Light-Directed, Spatially Addressable Parallel Chemical Synthesis*, 251 SCIENCE 767-773 (1991).
[5] James D. Watson et al., *Molecular Biology of the Gene* 550-594 (4th ed. 1987).

Gress "shows that despite the necessity of controls it is possible to quantify levels of gene expression by their method" (*id.* at 8).

The Examiner relies on Granelli-Piperno for disclosing "the effect of a variety of compounds on expression of genes of human cells," the "tested compounds includ[ing] cytokines, mitogens, cyclosporin A, and cycloheximide" (*id.* at 5). The Examiner finds that Granelli-Piperno discloses that the "RNA samples were resolved by electrophoresis and blotted to a membrane" (Figures 1-4, 8, and 9), that the "RNA was directly spotted as an array to a membrane" (Figures 5-7), that the "membrane was hybridized with labeled DNA of specific genes," and that the "response was determined by the intensity of a film image on an autoradiograph" (*id.*). The Examiner also finds that Granelli-Piperno "show[s] that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression and further serves to gain insights on the mechanism of action of the drug" (*id.*).

The Examiner relies on Fodor '98 for disclosing "a method of making an array of polynucleotide probes of predetermined sequence by independent in situ stepwise synthesis of each oligonucleotide probe on the array" (*id.*). The Examiner alternatively relies on Fodor '91 for disclosing "a method of synthesizing a dinucleotide of a predetermined sequence by a photo-lithographic process" and that "oligonucleotide arrays . . . could be made by their method" (*id.* at 6).

The Examiner concludes that it would have been obvious

> to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al. because Granelli-Piperno et

> al. shows that such an analysis serves to gain insights on the mechanism of action of the drug. The method of Gress et al. in which the treated cell cDNA is applied to an array of probes is an improvement over the assay method of Granelli-Piperno et al. in which a single gene is applied to RNA from the treated cell that is on a membrane because it allows for simultaneous assay of a large number of genes for effects of the drug on gene expression.

(*Id.*) The Examiner also concludes that it would have been obvious "to assay additional numbers of genes as desired to determine the effect of a drug on additional genes" (*id.*).

In addition, the Examiner concludes that it would have been obvious "to make and use an array of probes with a predetermined sequence made by the methods disclosed by Fodor et al. '98 or Fodor et al. '91" (*id.*). The Examiner finds that the use of pre-determined probe sequences provides "information about the molecules that hybridize to the array, as shown in Fodor '98 and Fodor '91" (*id.* at 8).

Appellants contend that the Examiner erred in concluding that claims 38 and 49 would have been obvious in view of Gress, Granelli-Piperno, and either Fodor '98 or Fodor '91.

FINDINGS OF FACT

1. Gress relates to "integrated mapping and sequencing analysis of genomes" (Gress 609).

2. Gress discloses "an approach allowing the characterization of large numbers of cDNA library clones with a minimal number of experiments" (*id.*).

3. Gress's approach comprises hybridizing cDNA pool probes derived from mouse tissue with a high-density cDNA library array and

analyzing the results "by conventional autoradiography and with a PhosphorImager" (*id.* at 609-611).

4. Gress discloses that "a PhosphorImager was used for evaluation of hybridization results and to transfer data into a computer database. This system was . . . more efficient in analyzing and comparing hybridization data." (*Id.* at 611-612.)

5. In particular, Gress discloses that the "[f]ilters were scanned on a PhosphorImager . . . for quantitative analysis of signal intensities. The scanned 16-bit images were stored in files . . . , transferred to a . . . computer, and analyzed." (*Id.* at 610.)

6. Gress also discloses that the "[h]ybridization results were stored in a relational database . . . together with the name of the corresponding cDNA clone and its microtiter plate location" (*id.* at 610-611).

7. In addition, Gress discloses that "[e]ach cDNA pool hybridization result was compared with data obtained from the control experiments on the same set of filters" and that the "results of hybridizations with cDNA pools derived from different tissues were analyzed as described and compared" (*id.* at 612).

8. Gress also discloses that a "relational database is necessary to establish correlations between results obtained in different fingerprinting and control experiments" (*id.* at 616).

9. In addition, Gress discloses that this system "allow[s] the screening of thousands of clones at a time" (*id.*).

10. Granelli-Piperno describes using "DNA-RNA blotting to . . . analyze the control of lymphokine mRNA levels. The initial goal was to use

a large panel of DNA probes to compare lymphokine and nonlymphokine gene expression in terms of kinetics, mitogen requirements, and sensitivity to [cyclosporin A]." (Granelli-Piperno 922.)

11. Granelli-Piperno states that the "results show that lymphokine and nonlymphokine mRNAs are induced by distinct exogenous stimuli" (*id.*).

12. In conducting the assay, Granelli-Piperno describes subjecting cell cultures to various stimuli, hybridizing on nitrocellulose filters nucleic acid derived from the stimulated cells with nucleic acid probes, and analyzing the results using autoradiography (*id.* at 923-924 & 930-931: Figs. 5-7).

13. Fodor '98 discloses "an ordered method for forming a plurality of polymer sequences by sequential addition of reagents" (Fodor '98, col. 2, ll. 47-50).

14. Fodor '98 discloses that the method "provides a composition comprising a plurality of positionally distinguishable sequence specific reagents attached to a solid substrate, which reagents are capable of specifically binding to a predetermined subunit sequence" (*id.* at col. 2, ll. 60-64).

15. Fodor '98 discloses using oligonucleotides as the sequence specific reagents (*id.* at col. 3, ll. 3-4).

16. In particular, Fodor '98 states that "an array of oligonucleotide probes of virtually any workable size may be positionally localized on a matrix and used to probe a sequence for either absolute complementary

matching, or homology to the desired level of stringency" (*id.* at col. 9, ll. 63-67).

17. In addition, Fodor '98 states that, "[b]ecause the oligonucleotide probes are positionally defined, the location of the hybridized duplex will directly translate to the sequences which hybridize" (*id.* at col. 4, ll. 57-59).

18. Fodor '91 discloses combining "[s]olid-phase chemistry, photolabile protecting groups, and photolithography . . . to achieve light-directed, spatially addressable parallel chemical synthesis to yield a highly diverse set of chemical products (Fodor '91, Abstract).

19. Fodor '91 discloses that "[h]igh-density arrays formed by light-directed synthesis are potentially rich sources of chemical diversity for discovering new ligands that bind to biological receptors and for elucidating principles governing molecular interactions" (*id.*).

20. Fodor '91 also discloses that "[o]ligonucleotide arrays produced by light-directed synthesis could be used to detect complementary sequences in DNA and RNA" and "would be valuable in gene mapping, fingerprinting, diagnostics, and nucleic acid sequencing" (*id.* at 772).

ANALYSIS

Gress describes a method for characterizing cDNA clones comprising detecting physical signals by contacting a nucleic acid array with cDNA derived from a living thing, transducing the physical signals into electrical output signals, storing the electrical output signals in digital form, and comparing the resulting data with control data and data from other tissues in a relational database (Findings of Fact (FF) 2-8). Gress discloses that this

method was "more efficient in analyzing and comparing hybridization data" (FF 4).

Granelli-Piperno describes a method for analyzing the effects of subjecting a living thing to a stimulus comprising detecting physical signals by contacting on nitrocellulose filters nucleic acid derived from the stimulated cells with nucleic acid probes and comparing the resulting data (FF 10-12). We agree with the Examiner that it would have been obvious to use the method described in Gress to analyze the effects of subjecting a living thing to a stimulus, as described in Granelli-Piperno, to increase the efficiency of the analysis.

Fodor '98 and '91 each describe techniques for forming oligonucleotide arrays having pre-determined nucleic acid sequences (FF 13-20). We agree with the Examiner with it would have been obvious to use such an array in the method described in Gress in order to analyze the effects of subjecting a living thing to a stimulus. By using a probe array rather than individual probes, the position of hybridization provides sequence information about the hybridized nucleic acid (FF 17).

Appellants argue that Gress "teaches away from the claimed invention because the method of Gress et al. is not suitable for measuring differences in gene expression and requires extensive use of controls due to the high level of background hybridization from polyA tails and repeated sequences" (App. Br. 12). In particular, Appellants argue that "it *appears* that the method of Gress et al. would not be suitable for the detection of low abundance transcripts in a cDNA library. Thus, it would not be suitable for measuring differences in gene expression and therefore would not provide

any expectation of success for use in the methods of the present invention." (*Id.* at 12-13 (emphasis added).)

In addition, Appellants "disagree with the Examiner's interpretation that the method of Gress et al. provides quantitative measurement of gene expression" (*id.* at 14). Appellants also assert that "Table 1 of Gress et al. demonstrates that the Gress et al. method is not suitable for *same-species* analysis due to the high background hybridization resulting from repetitive sequences" (Reply Br. 6; *see also* App. Br. 14-15). Therefore, Appellants argue that Gress "teaches away from comparing transcript levels of a panel of genes from stimulated and unstimulated cells derived from a subject, as claimed" (App. Br. 16).

We are not persuaded by these arguments. First, by teaching the use of controls (FF 7), Gress is clearly not teaching away from its own method, even if "extensive use of controls" is required. Second, Gress discloses that the "[f]ilters were scanned on a PhosphorImager . . . for quantitative analysis of signal intensities" (FF 5). Thus, Gress discloses that its method provides a quantitative measurement. Appellants have not provided sufficient evidence that one of ordinary skill in the art would not have expected Gress's method to be suitable for measuring differences in gene expression. In particular, even if Gress's method would not be suitable for same-species analysis, Appellants have not shown that, if Gress's method is modified to use an array having pre-determined sequences, as taught in the Fodor references, the method could not be used for same-species analysis.

Appellants also argue that Gress does not describe "the use of a matrix comprising a plurality of units wherein each unit confines a probe

comprising a predetermined sequence hybridizable with a different identified gene, transcript or cDNA derived from the gene of a living thing" (App. Br. 15). In contrast, Appellants argue that "it is apparent from the results in [Gress's] Table 1 that the nitrocellulose filters containing the cDNA pools described in Gress et al. contain numerous uncharacterized repetitive sequences and non-coding sequences that do not specifically hybridize to a transcript of an expressed gene" (*id.*).

However, the Examiner is not relying on Gress to teach these features. Instead, the Examiner is relying on the Fodor references to teach a probe matrix having a plurality of units wherein each unit confines a probe comprising a pre-determined sequence (Ans. 5-6). In addition, the Examiner is relying on Granelli-Piperno to teach probe sequences that are hybridizable with different identified genes of the living thing being analyzed (*id.* at 5). Therefore, we are not persuaded by Appellants' argument.

In addition, Appellants argue that "replac[ing] the thousands of unidentified cDNA clones that are arrayed on a nitrocellulose filter, or other substrate, as taught by Gress et al., with oligonucleotides having known sequences, would render the Gress et al. invention inoperable for its intended purpose" (App. Br. 19). Specifically, Appellants argue that in Gress the "strongly hybridizing clones are selected for sequencing. . . . [I]t would be illogical to use probes of known sequence in order to determine which of the probes of known sequence will be sequenced." (*Id.*) Appellants also argue that this modification "would only permit an investigator to identify the expression pattern of those clones in the pool that happen to hybridize to one of the pre-determined sequences" (*id.* at 19-20). Consequently, Appellants

argue that it would not have been obvious "to modify the Gress et al. method by incorporating the teachings of the Fodor et al. publication" (*id.* at 20). (*See also* App. Br. 16-17 & 23-24.)

We are not persuaded by these arguments. Gress describes using its techniques for "integrated mapping and sequencing analysis of genomes" (FF 1). However, the Examiner is not relying on Gress for teaching techniques for mapping and sequencing genomes. Instead, the Examiner is relying on Gress for teaching a computerized approach to the analysis of hybridization assays (Ans. 4). Thus, the Examiner is not arguing that it would have been obvious to use a sequenced array in the genome mapping and sequencing technique described in Gress. Instead, the Examiner concludes that it would have been obvious to use the arrays of known oligonucleotides probes (*see* FF 15-17) as taught in the Fodor references and the computer analysis technique described in Gress in order to analyze the effects of subjecting a living thing to a stimulus, as described in Granelli-Piperno (Ans. 6-7). Appellants have not shown that this combination of references is improper.

In addition, Appellants argue that "impermissible hindsight reconstruction has been used to improperly combine elements from Gress et al. and Fodor et al. '98 or '91" (App. Br. 11). In particular, Appellants argue that "the purpose and focus of the Gress et al. and Fodor et al. publications are quite different, and that when the two publications are each read as a whole, there is no motivation to combine them, or to select individual elements of the disclosure of each of these publications and combine them" (*id.* at 21).

We are not persuaded by this argument. Instead, we agree with the Examiner that one of ordinary skill in the art would have been motivated to combine these references with Granelli-Piperno for the reasons discussed above.

Appellants also argue that "the teachings of Granelli-Piperno et al. and either Fodor et al '98 or Fodor '91 fail to cure the deficiencies of Gress" (App. Br. 11). In particular, Appellants argue:

> Granelli-Piperno et al. fails to teach or suggest at least the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a predetermined sequence hybridizable with a different identified gene, transcript or cDNA derived from the gene of a living thing, or storing in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus; and (ii) with the identity of the identified gene, as claimed. In sharp contrast to the claimed invention, the methods described in Granelli-Piperno et al. relate to the use of a nitrocellulose filter containing total cellular RNA isolated from T cells that is hybridized with individual probes specific to nine genes known to be involved in T cell stimulation.

(*Id.* at 22.) (*See also* App. Br. 24.)

We are not persuaded by this argument. First, the Fodor references describe the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a pre-determined sequence (FF 13-20). Based on the teachings in the Fodor references, we agree with the Examiner that it would have been obvious to hybridize nucleic acids isolated from a living thing to a matrix comprising a plurality of units wherein each unit confines a probe comprising a pre-determined sequence rather than hybridizing individual probes to a matrix containing nucleic acids from a living thing, as

taught in Granelli-Piperno. As discussed above, by using a probe array rather than individual probes, the position of hybridization provides sequence information about the hybridized nucleic acid (FF 17). In addition, by using the techniques described in Gress, thousands of clones can be screened at a time (FF 9).

Second, Gress describes storing the hybridization results in a relational database "together with the name of the corresponding cDNA clone and its microtiter plate location" (FF 6). Based on this teaching, we agree with the Examiner that it would have been obvious, in the combined method, to store in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus and (ii) with the identity of the identified gene.

We conclude that the Examiner has set forth a prima facie case that claim 38 would have been obvious over Gress, Granelli-Piperno, and either Fodor '98 or Fodor '91, which Appellants have not rebutted. We therefore affirm the rejection of claim 38 under 35 U.S.C. § 103(a) over these references. Claims 39-48, 52, 53, 55-62, 66, 68-79, 83, and 85 have not been argued separately and therefore fall with claim 38. 37 C.F.R. § 41.37(c)(1)(vii).

With regard to claim 49, Appellants additionally argue that none of the applied references teach or suggest "to detect physical signals from a plurality of units ordered in a probe matrix, wherein each unit confines a probe comprising a pre-determined sequence that is hybridizable to at least 0.5% of the genes of the living thing, in order to analyze the effects of

subjecting a living thing to a stimulus" (App. Br. 23). In particular, Appellants argue:

> Granelli-Piperno et al. only teaches studying the effect of the stimulus on the expression of a small subset of genes in a cell. The proposed motivation by the Examiner to modify the referenced teachings to assay additional numbers of genes does not derive from the references themselves. . . . Rather, Granelli-Piperno et al. is a directed study specifically designed to analyze the effect of cyclosporin A on a set of nine different lymphokine mRNA levels.

(*Id.*) Therefore, Appellants argue that "absent some suggestion to assay a wider array of genes, such as at least 0.5% of the genes of a living thing, to measure the effect of a stimulus on a living subject, there is no motivation or expectation of success to attempt to modify the method of Gress et al. with the teachings of Granelli-Piperno" (*id.*)

We are not persuaded by this argument. First, the motivation to modify a reference need not come from the references themselves. As recently indicated by the Supreme Court, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007). In the present case, the Examiner finds that persons of ordinary skill in the art would have been prompted "to assay additional numbers of genes as desired to determine the effect of a drug on additional genes" (Ans. 6). Appellant have not shown that this finding is incorrect.

We conclude that the Examiner has set forth a prima facie case that claim 49 would have been obvious over Gress, Granelli-Piperno, and either Fodor '98 or Fodor '91, which Appellants have not rebutted. We therefore

affirm the rejection of claim 49 under 35 U.S.C. § 103(a) over these references. Claims 50, 51, 63-65, and 80-82 have been argued as a group with claim 49 (App. Br. 23) and therefore fall with claim 49. 37 C.F.R. § 41.37(c)(1)(vii).

With regard to the rejection over Gress, Granelli-Piperno, either Fodor '98 or Fodor '91, and Watson, Appellants argue that Watson does not cure the deficiencies of the other references (App. Br. 25). However, we have already concluded that claims 38 and 49 would have been obvious over Gress, Granelli-Piperno, and either Fodor '98 or Fodor '91. Thus, we are not persuaded by Appellants' argument. We therefore affirm the rejection of claims 38 and 49 under 35 U.S.C. § 103(a) over Gress, Granelli-Piperno, either Fodor '98 or Fodor '91, and Watson. Claims 50, 51, 54, 56, 63-65, 67, 70, 80-82, and 84 have not been argued separately and therefore fall with claims 38 and 49.

CONCLUSION

The Examiner's position is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 38-85 under 35 U.S.C. § 103(a).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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